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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,036	02/09/2005	Maharaj K. Sahib	WH-2	1841
7590	10/05/2007	O M (Sam) Zaghmout Bio Intellectual Property Services (Bioips) 8509 Kerner Ct Lorton, VA 22079	EXAMINER WOODWARD, CHERIE MICHELLE	
			ART UNIT 1647	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/524,036	SAHIB ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 09 February 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 12-22 and 29-36 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-11 and 23-28 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 09 February 2005 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) Notice of Informal Patent Application
- 6) Other: \_\_\_\_\_.

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**DETAILED ACTION*****Election/Restrictions***

1. Applicant's election with traverse of Group I (claims 1-11 and 23-28) in the reply filed on 20 July 2007 is acknowledged. The traversal is on the ground(s) that all three groups related to a single inventive concept. Applicant relies on MPEP 806.05(i), 808, and 808.02. This is not found persuasive because the instant application is a national stage application filing under 35 USC 371 and comprises multiple products and processes. As was stated in the Requirement for Restriction/Election, pursuant to 37 CFR 1.475, a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. 37 CFR 1.476 (1)(d) states that if multiple products, processes or manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims (see PCT Article 17(3)(a) and 37 CFR 1.476(c)). In the instant case, because multiple products and multiple processes of making the different products are claimed, the first recited invention was formulated as Group I. Group I includes the first product, the first method of making, and the first method of using. The DNA construct of Group I is the first claimed product and the polypeptide of Group II is the second product. Accordingly, the main invention (Group I) comprises the first claimed product, which is the DNA construct (claims 1-11, 23-24, and 28) and the method of making the first product (claims 25-27) (see also, MPEP 1850).

The requirement is still deemed proper and is therefore made FINAL.

***Formal Matters***

2. Claims 1-36 are pending. Claims 12-22 and 29-36 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 20 July 2007. Claims 1-11 and 23-28 are under examination.

***Claim Objections***

3. Claim 1 is objected to because of the following informalities: the word "hormone" is misspelled as "harmone" in line 6 of claim 1. Appropriate correction is required.

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***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-11 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markusen et al., US Patent 4,962,212 (10 April 1990) and Schweden et al., US Patent 5,672,487 (30 September 1997).

The Examiner finds the following facts:

- a. The claims are drawn to a DNA construct with the formula pY-SP-B(1-29)-A(1-21), wherein the promoter is a yeast promoter, wherein SP encodes a signal peptide from the recited species of *Schwanniomyces occidentalis* glucoamylase signal peptide sequence or from *Carcinus maenal* crustacean hyperglycemic hormone signal peptide sequence, B(1-29) and A(1-21) are from the coding sequences of an insulin pre-pro-peptide, linked by means of a peptide bond;

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wherein the construct does or does not carry a kex protease cleavage site; wherein the construct comprises a single methionine residue at the N-terminus of the B(1-29)-A(1-21) region; wherein the SP has either a single arginine or a single lysine residue adjacent to the N-terminus of the polypeptide encoded by the B(1-29)-A(1-21) sequence; wherein the insulin pre-pro-peptide is human insulin; a process for the expression of insulin in yeast with the construct of claim 1; made by a process a yeast promoter selected from MOX-P, FMDH-P, FMD-P, or DHAS-P; wherein the yeast is selected from the genera *Hansenula*, *Saccharomyces*, *Pichia*, and *Kluveromyces*; wherein the species is *Hansenula polymorpha*.

b. The '212 patent teaches DNA constructs comprising human insulin precursors containing the peptide chain B(1-29)-A(1-21) of human insulin with a bridging chain connecting the carboxyl terminus of the B(1-29)-chain with the amino terminus of the A(1-21)-chain, by the formula  $B(1-29)-(X_n-Y)_m-A(1-21)$  [referred to as formula I], where n is an integer from 0 to 33 and m is 0 or 1 (column 2, lines 54-67 to column 3, lines 1-11) (compare instant claim 1). Formula I where m is 0 (meaning that there is no linker other than a direct peptide bond between B(1-29) and A(1-21)) is taught at column 3, lines 8-11 and claims 1 and 2 (compare instant claim 1). The DNA construct is prepared by culturing a yeast host transformed with a replicable expression vehicle capable of expressing a DNA-sequence encoding the insulin precursor (column 3, lines 20-23; column 4, lines 48-60) (compare instant claim 25). Expression using a yeast promoter is taught at column 4, lines 57-58. Secretion using a leader sequence is taught at column 4, lines 40-47) (compare instant claims 1 and 23). A method for preparing human insulin is taught whereby a yeast strain is transformed with a replicable expression vehicle comprising a DNA-sequence encoding the insulin precursors of the recited formula I the transformed yeast strain is cultured in a suitable nutrient medium, the insulin precursors are recovered from the culture medium and converted in vitro into human insulin (column 4, lines 63-68 to column 5, lines 1-2) (compare instant claim 25). The '212 patent teaches the addition of selective cleavage site adjacent to the N-terminal of the B(1-29)-chain of the insulin precursors enabling subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatical or chemical cleavage (column 3, lines 60-64) (compare instant claims 4-11). Cleavage at a methionine adjacent to the desired protein is taught at column 4, lines 25-26 (compare instant claims 8 and 9). Arginine and lysine cleavage sites adjacent to the desired protein enables cleavage with trypsin-like proteases (column 4, lines 26-28) (compare instant claims 10 and 11). When the insulin precursor is expressed in yeast the sequence may contain two basic amino acids

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(e.g. Lys-Arg or Arg-Lys) adjacent to N-terminal of the B(1-29)-chain of the insulin precursor, because yeast are able to cleave the peptide bond between the basic amino acids and the precursor (column 4, lines 9-14) (compare instant claims 10 and 11). [Examiner note: because instant claims 10 and 11 recite the word "has" following the preamble, the Examiner interprets "has" as "comprises." The claim is read as "comprises either a single arginine or a single lysine residue..." Because of the open-ended claim terminology, claims 10 and 11 do not exclude the use of a dipeptide arg-lys or lys-arg, so long as there is only one lys or one arg. See also MPEP 2111 and 2111.03.]

c. The '212 patent does not teach the DNA construct with signal sequences from the species of *Schwanniomyces occidentalis* glucoamylase or *Carcinus maenal* crustacean hyperglycemic hormone.

d. The '487 patent teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha* (entire document, especially Example 1, column 3; and Example 2, column 4) (compare instant claims 25, 26, and 27). The glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is taught as an applicable signal peptide (column 1, lines 28-30) (compare instant claims 1 and 2) and the leader sequence from the hyperglycemic hormone of the shore crab, which consists of residues 1-26 of SEQ ID NO: 1 (column 1, lines 64-67) (compare instant claims 1 and 3). The shore crab signal sequence taught by the '487 patent is identical to the signal sequence of the crustacean hyperglycemic hormone (CHH) from *Carnius maenas* (see, for exemplary purposes only, Weidemann et al., (FEBS Lett. 1989. Oct 23; 257(1):31-4) (see also, column 1, lines 62-64, citing the Weidemann et al., reference). The '487 patent also teaches the KEX2 processing signal recognition site from *Saccharomyces*, which consists of the dipeptide Lys-Arg and is also recognized by other yeasts (column 2, lines 32-34) (compare instant claims 4-7, 10, and 11). MOX and FMD promoters are taught in Example 4 (column 5, line 22) (compare instant claim 24). Yeasts of the genera *Hansenula*, *Saccharomyces*, *Kluyveromyces*, and *Pichia* are taught in claim 3 (compare instant claim 26).

e. Yeasts of the genera *Hansenula* and *Pichia* are methylotropic yeasts (see, for exemplary purposes only Hollenberg et al., (Curr Opin Biotechnol. 1997 Oct;8(5):554-60, Abstract Only).

f. The level of skill of those in the art encompasses skills in the field of molecular biology relating to the construction or generation of DNA constructs in yeasts by standard and routine methodologies.

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g. A person of ordinary skill in the art at the time the invention was made would have reasonably known that DNA constructs could be made in yeasts by using known promoter sequences, known signal proteins for optimal/high efficiency protein expression, and the known pre-pro peptide sequence of insulin, human or of non-human origin. Further, a person of ordinary skill in the art would have been able to make the DNA construct merely by using well-known methodologies and protocols, such as the ones taught by the '212 patent and the '487 patent, and the resulting structure of the DNA construct and expression of insulin proteins therefrom would have been predictable.

In view of the facts recited above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention.

The '212 patent teaches DNA constructs comprising human insulin precursors containing the peptide chain B(1-29)-A(1-21) of human insulin with a bridging chain connecting the carboxyl terminus of the B(1-29)-chain with the amino terminus of the A(1-21)-chain, by the formula B(1-29)-(X<sub>n</sub>-Y)<sub>m</sub>-A(1-21) [referred to as formula I], where n is an integer from 0 to 33 and m is 0 or 1 (column 2, lines 54-67 to column 3, lines 1-11) (compare instant claim 1). Formula I where m is 0 (meaning that there is no linker other than a direct peptide bond between B(1-29) and A(1-21)) is taught at column 3, lines 8-11 and claims 1 and 2 (compare instant claim 1).

The DNA construct is prepared by culturing a yeast host transformed with a replicable expression vehicle capable of expressing a DNA-sequence encoding the insulin precursor (column 3, lines 20-23; column 4, lines 48-60) (compare instant claim 25). Expression using a yeast promoter is taught at column 4, lines 57-58. Secretion using a leader sequence is taught at column 4, lines 40-47) (compare instant claims 1 and 23). A method for preparing human insulin is taught whereby a yeast strain is transformed with a replicable expression vehicle comprising a DNA-sequence encoding the insulin precursors of the recited formula I the transformed yeast strain is cultured in a suitable nutrient medium, the insulin precursors are recovered from the culture medium and converted in vitro into human insulin (column 4, lines 63-68 to column 5, lines 1-2) (compare instant claim 25).

The '212 patent teaches the addition of selective cleavage site adjacent to the N-terminal of the B(1-29)-chain of the insulin precursors enabling subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatical or chemical cleavage (column 3, lines 60-64) (compare instant claims 4-11). Cleavage at a methionine adjacent to the desired protein is taught at

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column 4, lines 25-26 (compare instant claims 8 and 9). Arginine and lysine cleavage sites adjacent to the desired protein enables cleavage with trypsin-like proteases (column 4, lines 26-28) (compare instant claims 10 and 11). When the insulin precursor is expressed in yeast the sequence may contain two basic amino acids (e.g. Lys-Arg or Arg-Lys) adjacent to N-terminal of the B(1-29)-chain of the insulin precursor, because yeast are able to cleave the peptide bond between the basic amino acids and the precursor (column 4, lines 9-14) (compare instant claims 10 and 11). [Examiner note: because instant claims 10 and 11 recite the word "has" following the preamble, the Examiner interprets "has" as "comprises." The claim is read as "comprises either a single arginine or a single lysine residue..." Because of the open-ended claim terminology, claims 10 and 11 do not exclude the use of a dipeptide arg-lys or lys-arg, so long as there is only one lys or one arg. See also MPEP 2111 and 2111.03.]

The '487 patent teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha* (entire document, especially Example 1, column 3; and Example 2, column 4) (compare instant claims 25, 26, and 27). The glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* is taught as an applicable signal peptide (column 1, lines 28-30) (compare instant claims 1 and 2) and the leader sequence from the hyperglycemic hormone of the shore crab, which consists of residues 1-26 of SEQ ID NO: 1 (column 1, lines 64-67) (compare instant claims 1 and 3). The shore crab signal sequence taught by the '487 patent is identical to the signal sequence of the crustacean hyperglycemic hormone (CHH) from *Carnius maenas*, as exemplified by Weidemann et al., (FEBS Lett. 1989. Oct 23; 257(1):31-4) (see also, column 1, lines 62-64, citing the Weidemann et al., reference). The '487 patent also teaches the KEX2 processing signal recognition site from *Saccharomyces*, which consists of the dipeptide Lys-Arg and is also recognized by other yeasts (column 2, lines 32-34) (compare instant claims 4-7, 10, and 11). MOX and FMD promoters are taught in Example 4 (column 5, line 22) (compare instant claim 24). Yeasts of the genera *Hansenula*, *Saccharomyces*, *Kluyveromyces*, and *Pichia* are taught in claim 3 (compare instant claim 26).

The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a DNA construct with the instantly recited limitation. One of skill in the art would have recognized that the results of the combination of a yeast promoter, a well-known signal peptide from either of the recited species, a human or animal insulin pre-pro peptide sequences, with or without a Kex protease cleavage site, with or without a single methionine residue, a single arginine residue, or a single lysine residue at the N-terminal of the pre-pro-insulin peptide, a process of using a well-known yeast promoters MOX and FMD, by transforming yeasts, including the genera *Hansenula*, *Saccharomyces*, *Pichia*, and *Kluyveromyces*, and the species *Hansenula polymorpha* with a plasmid carrying the DNA

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construct, expressing the transformed yeasts in culture, and isolating the insulin containing polypeptide from the culture would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made. It would have also been obvious to use the MOX (methanol oxidase) promoter, for example, in methylotropic yeasts, such as *Hansenula polymorpha* and *Pichia* species. It is noted that each of the Kex site, methionine precursor, arginine and lysine precursors are all equivalent alternative cleavage sites in the processing of peptides in yeasts, as taught by both the '212 and the '487 patents. This is demonstrated by the fact that DNA constructs meeting all of the claim limitations and methods of making them are taught by the '212 and the '487 patents.

***Conclusion***

2. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
  - a. Magota et al., US Patent 5,885,821 (23 March 1999) teaches DNA constructs comprising Kex2 protease derivatives obtained by transforming methanol-assimilating yeasts with expression vectors containing DNA coding for any amino acid sequence.
  - b. Kjeldsen et al., US Patent 6,521,738 (18 February 2003, benefit to 10 February 2000) teaches DNA constructs comprising insulin precursor molecules expressed in transformed yeasts.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Gary Nickol/

Gary Nickol  
Supervisory Patent Examiner, Art Unit 1646